Tetrahedron Letters 50 (2009) 5067–5070

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Preparation of vinylglycines by thermolysis of homocysteine sulfoxides

Sravan Kumar Patel [a], Timothy E. Long [a,b,*]

[a] The Department of Pharmaceutical and Biomedical Sciences, University of Georgia, Athens, GA 30602-2352, USA
[b] Center for Drug Discovery, University of Georgia, Athens, GA 30602-2352, USA

ARTICLE INFO

Article history:
Received 30 April 2009
Revised 3 June 2009
Accepted 16 June 2009
Available online 21 June 2009

ABSTRACT

The synthesis and efficacy of preparing Cbz-VG-OMe (**1**) by thermolysis of alkyl and aryl homocysteine sulfoxides were surveyed. This investigation determined that aryl sulfoxide analogs were more effective for the reaction and that the 2-nitrophenyl analog **10f** possessed a unique ability to syn eliminate at temperatures as low as 100 °C. The thermolysis of sulfoxide **10f** was additionally discovered to occur under toluene reflux and when sodium acetate was added, Cbz-VG-OMe (**1**) could be obtained in high purity by simple filtration of the precipitated sulfenic acid byproduct **12**. This mild protocol which was also applied in the synthesis of VG dipeptide **13** would have utility in the general synthesis of olefins and alkenes from 2-nitrophenylsulfoxides.

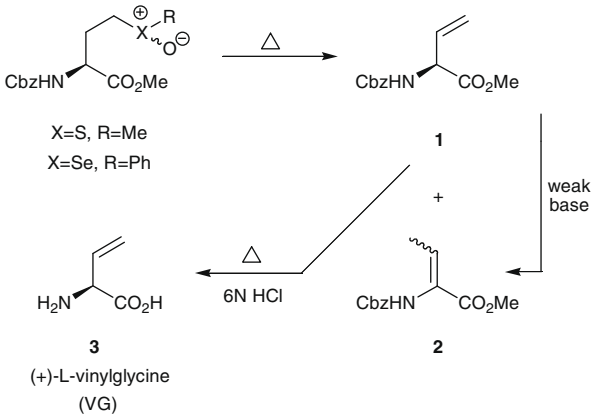
Published by Elsevier Ltd.

1. Introduction

Vinylglycine[1] (VG) is a natural, non-protein α-amino acid which acts as an inhibitor of enzymes with the pyridoxal phosphate (PLP) cofactor such as alanine racemase,[2] aspartate aminotransferase,[3] and α-ketoglutarate dehydrogenase.[4] As a useful tool for studying mechanism-based deactivation of pyridoxal enzymes,[1] efforts have been made to identify other β,γ-unsaturated amino acids in nature. In addition, protected forms of VG have had synthetic utility in the preparation of metabotropic glutamate receptors agonists,[5] poly-γ-glutamate synthetase inhibitors,[6] and the antitumor antibiotic (+)-FR900482.[7]

Traditionally, the methods of choice to synthesize L-VG have been by pyrolysis of protected methionine sulfoxide (MetO)[8] and thermolysis of aryl selonoxides (Scheme 1) obtained from either protected L-glutamate,[9] L-homoserine,[10] or L-homoserine .[11] For multi-gram syntheses, the MetO pyrolysis approach is most commonly implemented; however due to the high vacuum (⩽3 mmHg) and temperature (>150 °C) requirements, isomerization is a consistent problem for the reaction.[8] The migratory occurrence to the more thermally stable β-methyldehydroalanine (i.e., **2**) is further enhanced by the acidity of the α-proton in N,O-protected forms of VG (i.e., **1**). The isomer will form quantitatively in the presence of triethylamine or *N*-methylmorpholine[8] and it is likewise believed that this decomposition during purification on silica contributes to an optimized yield of 60%.[12]

Due to the difficult chromographic separation of the α,β-isomers from protected vinylglycines and our desire to find a non-pyrolytic approach, we wanted to identify alternative sulfinyl substituents that would facilitate the syn elimination at temperatures below 150 °C. This Letter describes: (i) the preparation of unreported (*S*)-homocysteine (Hcy) sulfides and sulfoxides (HcyO); (ii) the syn elimination efficacy of *S*-alkyl- and *S*-aryl-substituted HcyO esters; and (iii) a new protocol to generate olefins in high purity from 2-nitrophenyl sulfoxides under mild toluene reflux.



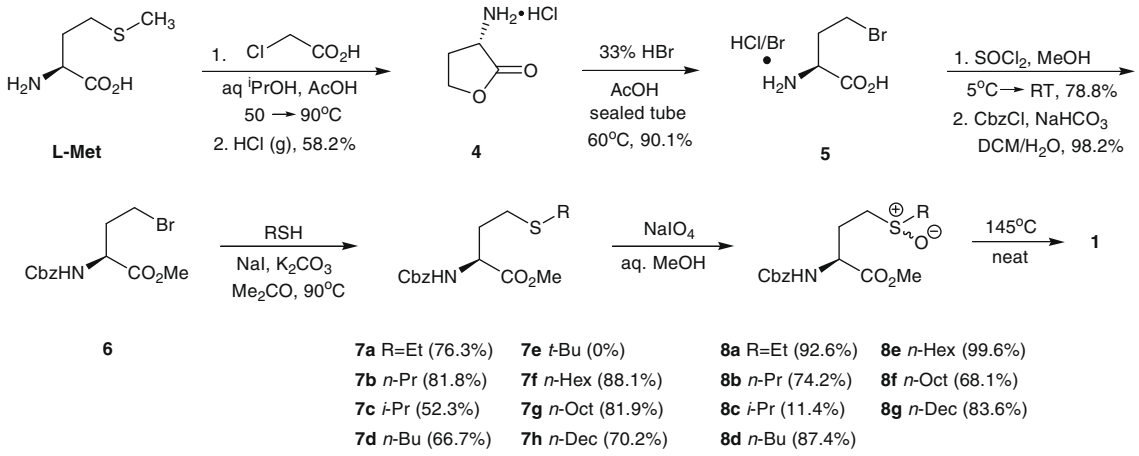
Scheme 1. Reported preparations of L-vinylglycine (VG).

2. Results and discussion

The investigation began by examining the thermolysis of MetO analogs with longer alkyl chains. The sulfoxides were synthesized via the thiolation and oxidation of (*S*)-bromoethylglycine **6**

* Corresponding author. Tel.: +1 706 542 8597; fax: +1 706 542 5358.
E-mail address: tlong@rx.uga.edu (T.E. Long).

0040-4039/$ - see front matter Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2009.06.082



Scheme 2. Preparation of HcyO(alkyl) esters **8**.

(Scheme 2). Its precursor, the mixed bromide salt **5**,[13] was obtained in 2 steps by the hydrobromination of (*S*)-homoserine lactone HCl (**4**) followed by N,O-protection with –Cbz and –Me, respectively. The Hcy(alkyl) esters **7** were next prepared by nucleophilic thiolation of bromide **6** under Finkelstein conditions.[14] Reactions were performed in a sealed tube to prevent thiol evaporation and alkyl sulfides **7** were obtained in 52–88% yield with the exception of protected Hcy(*tert*-butyl) **7e** which failed to form by this method. Oxidation of the sulfides by aqueous sodium periodate provided HcyO(alkyl) esters **8a–g** as a mixture of diastereomers for the elimination studies.

The reactions were conducted for each sulfoxide at 145 °C in order to minimize isomerization. ^{1}H NMRs were taken daily over a 3-day period to monitor the progress of the solventless experiments and to provide ratio estimates of (*S*)-Cbz-VG-OMe (**1**), α,β-unsaturated isomer (**2**), and starting materials (**8a–g**). As anticipated, the syn elimination rate of Cbz-MetO-OMe[8] was found to be appreciably less than that for the multi-carbon chain analogs (Table 1). The highest yield of these was HcyO(*n*-Bu) ester **8d**; however a common theme among all the alkyl sulfoxides was the slow elimination at 145 °C. In addition, the exposure of VG **1** to heat over 72 h appeared to increase isomer formation and the duration of the thermolysis needed to be substantially reduced in order to optimize the reaction. This could be accomplished by raising the temperature to 190 °C as observed for HcyO(*n*-Bu) **8d** although isolated yields were typically lower presumably due to decomposition on the silica.

Table 1
Syn elimination results of HcyO(alkyl) esters **8**

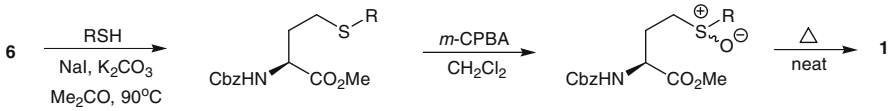
R=	°C	Time (h)	mmHg	**1**:**2**:**8**[a]	Yield[b] (%)
Me[8]	145	72	760	0.3:0:1	12.3[c]
Me[8]	190	2	760	1:0.7:0.7	1.2[c]
Et (**8a**)	145	72	760	0.8:.03:1	—
n-Pro (**8b**)	145	42	760	0.6:0.1:1	—
n-Pro (**8b**)	145	72	760	0.5:0.4:1	45.7
i-Pro (**8c**)	145	72	760	0.2:0:1	—
n-Bu (**8d**)	145	42	760	0.8:0.1:1	—
n-Bu (**8d**)	145	72	760	0.7:0.3:1	49.8
n-Bu (**8d**)	190	5	3	1:0:0.2	30.3
n-Hex (**8e**)	145	72	760	1:0:0.8	35.1
n-Oct (**8f**)	145	72	760	1:0.1:0.7	18.2
n-Dec (**8g**)	145	72	760	1:0.1:1.4	41.3

[a] Est. based on integrations in crude ^{1}H NMR.
[b] Isolated yield.
[c] Contained isomer **2**.

Attention was turned next to examining the elimination reaction of aryl sulfoxides **10**. The (*S*)-Hcy(aryl) analogs were prepared from bromide **6** in the same manner described followed by oxidation with *m*-CPBA which afforded higher yields than sodium periodate (Scheme 3). The elimination studies (Table 2) revealed a greater syn thermolysis rate for the phenyl sulfoxides than their HcyO(alkyl) counterpart. First evaluated was HcyO(Ph) **10b** which after 18 h decomposed to the desired olefin **1** along with small amounts of α,β-isomer **2** and deoxygenated Hcy(Ph) **9b**. Chromatography purification on silica however yielded only 54.1% of pure (*S*)-Cbz-VG-OMe. Additional reactions were performed on HcyO(Ph) **10b** to screen alternative conditions and each were found to increase reduced side product **9b** formation including: reduced pressure (3 mmHg); reflux in DMF; microwave; and higher temperature (190 °C/0.25 h). At temperatures less than 140 °C, the elimination rate diminished substantially and deoxygenated side product increased proportionally to longer durations of heat exposure.

Comparable results were observed for substituted phenyl analogs with the exception of HcyO(*p*-MeOPh) **10c** which appeared to have the greatest susceptibility to side product formation (Table 2). This was not unexpected as preceding research on the pyrolysis of substituted aryl sulfoxides deduced a correlation between elimination rate and phenyl ring substituents. Emerson[15] established that *para*-situated electron-donating groups (i.e., MeO, Me) slowed the pyrolysis of aryl *n*-propyl sulfoxides while electron-withdrawing moieties (i.e., Cl, NO_2) enhanced the rate. The substitution effect was indeed apparent for the HcyO(aryl) **10c–f** with HcyO(*p*-MeOPh) **10c** as the lone analog with unconverted sulfoxide remaining after 18 h. The thermolysis of HcyO(*p*-ClPh) and HcyO(*p*-NO_2Ph) esters **10d** and **10e**, respectively, was complete within this period with only traces of isomer present. It was also determined that the time of thermolysis could be reduced to 15 min by applying a temperature of 190 °C with limited side product formation.

The influence of electron-withdrawing groups on the syn elimination of aryl selenoxides was similarly examined by Sharpless and Young.[16] Their studies revealed that a nitro group located *ortho* substantially accelerated the reaction causing decomposition to *o*-nitrophenyl selenenic acid and 1-dodecene at 25 °C. This prompted us to evaluate the thermolysis rate of HcyO(*o*-NO_2Ph) **10f** which required preparation of 2-nitrothiophenol (**11**) via Ph_3P-mediated reduction of its commercial disulfide. Upon heating at 145 °C, decomposition of sulfoxide **10f** was observed within minutes and after 1 h the thermolysis was complete. NMR analysis of the crude product revealed complete conversion to the desired VG ester **1** and absence of both isomer and deoxygenated side products. The



9a R=Bn
9b Ph (89.0%)
9c *p*-MeOPh (45.6%)
9d *p*-ClPh (77.8%)
9e *p*-NO_2Ph (62.2%)
9f *o*-NO_2Ph (94.9%)

10a R=Bn (54.1%, 2 steps)
10b Ph (89.1%)
10c *p*-MeOPh (89.6%)
10d *p*-ClPh (95.8%)
10e *p*-NO_2Ph (62.7%)
10f *o*-NO_2Ph (95.3%)

Scheme 3. Preparation of HcyO(aryl) analogs **10**.

Table 2
Syn elimination results of HcyO(aryl) esters **10**

R=	°C	Time (h)	mmHg	**1**:**9**:**10**[a]	Yield[b] (%)
Bn (**10a**)	145	72	760	0.6:0:1	29.9
Bn (**10a**)	145	10	3	0.1:0:1	—
Ph (**10b**)	145	18	760	1:0.1:0	54.1
Ph (**10b**)	145	10	3	1:0.3:0.3	57.9
Ph (**10b**)	190	0.25	760	1:0:0.3[c]	25.0
p-MeOPh (**10c**)	145	18	760	1:0.4:0.2	35.5
p-MeOPh (**10c**)	190	0.25	760	1:0.4:0.2[c]	9.2
p-ClPh (**10d**)	145	18	760	1:0:0[c]	41.0
p-ClPh (**10d**)	190	0.25	760	1:0.1:0[c]	67.0
p-NO_2Ph (**10e**)	145	19	760	1:0:0[c]	53.9
p-NO_2Ph (**10e**)	190	0.25	760	1:0:0	62.9
o-NO_2Ph (**10f**)	145	0.25	760	1:0:1.3	—
o-NO_2Ph (**10f**)	145	1	760	1:0:0	35.5
o-NO_2Ph (**10f**)	100	18	760	1:0:2.8	—

[a] Est. based on relative ^{1}H peak areas in crude NMR.
[b] Isolated yield.
[c] Contained isomer **2**.

crude material was chromatographed on silica to provide pure Cbz-VG-OMe in 35.5% yield.

Temperatures as low as 100 °C were additionally found to catalyze the thermolysis of the *o*-nitrophenyl analog **10f** and the reaction was further evaluated under reflux conditions. Different solvents were screened including chloroform and benzene; however higher boiling non-polar, aprotic solvents such as toluene were required to complete the transformation. A serendipitous finding of the reaction came with precipitation of the sulfenic acid **12** byproduct which was water-soluble and could be removed by filtration. Unfortunately, a small portion of this acid decomposed into several toluene-soluble impurities and we began exploring conditions that avoided this outcome.

Methods to neutralize sulfenic acid **12** and prevent its decomposition were evaluated using various bases. Reactions supplemented with pyridine, $NaHCO_3$, and K_2CO_3 were effective but each catalyzed partial isomerization. Conversely, the addition of NaOAc (Scheme 4) negated impurity formation while permitting facile removal of the sulfenic acid precipitate by filtration through Celite. ^{1}H NMR analysis of the toluene filtrate revealed >99% conversion to VG ester **1** and the absence of side products. Substitution with higher boiling chlorobenzene was also found to reduce reaction time to under 6 h; however prolonged reflux (>10 h) resulted in minor amounts of isomer in the filtered product.

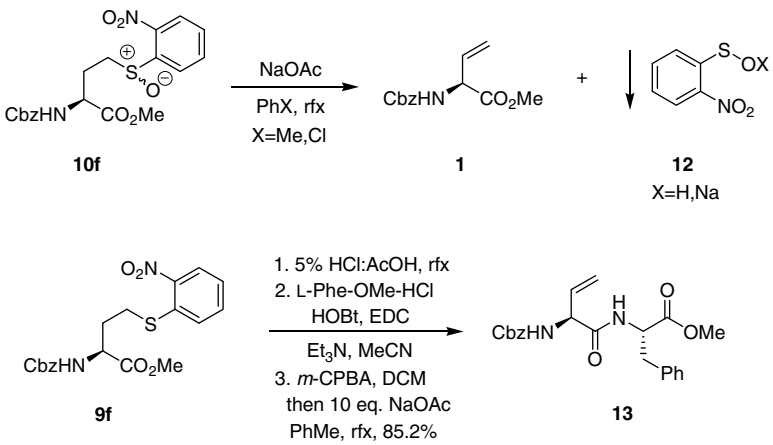
A utility of this protocol was next applied toward the synthesis of the dipeptide L-Cbz-VG-Phe-OMe (**13**). The preparation began with saponification of sulfide **9f** followed by an EDC-mediated coupling of the resulting acid with L-Phe-OMe. S-Oxidation with *m*-CPBA and thermolysis of the sulfoxide under toluene reflux resulted in precipitation of the acid **12** byproduct while providing vinyl dipeptide **13** in 85.2% isolated yield.

3. Conclusion

The described study found that the 2-nitrophenylsulfoxide **10f** can serve as an effective alternative to aryl selenoxides in the thermolytic preparation of VG **1**. With this precursor, it is likewise possible to avoid problems of isomerization without selenide use while the ability to obtain essentially pure compound via filtration of the sulfenic acid **12** byproduct is an added advantage. This protocol is also being applied in our laboratory to generate other types of olefins and alkenes in high purity from 2-nitrophenylsulfoxides. Typically, elimination reactions utilizing sulfoxides involve the use of strong base and/or heat that can result in low yields. This first report on the unique eliminating

Before reflux

NaOAc suspended in a PhMe solution of the 2-nitrosulfoxide.Yellow coloration of the solution is due to the nitrophenyl group.



After reflux

Acid **12** absorbs onto the NaOAc turning it brown. The solution containing the olefin is colorless due to precipitation of the nitrophenyl by product **12**.

Scheme 4. Preparation of vinylglycines from 2-nitrophenylsulfoxides.

properties of 2-nitrophenylsulfoxides has demonstrated that they can be employed as an efficient replacement to selenoxides in the preparation of molecules containing a heat- or oxidant-sensitive olefin.

Acknowledgments

Financial support of this work was provided by the University of Georgia and the Hayes' endowment fund. Special thanks are given to the Department of Pharmaceutical and Biomedical Sciences NMR facilities, Dr. Dennis Phillips for mass spectroscopy analyses, and Dr. Warren Beach for helpful discussion.

Supplementary data

Supplementary data (experimental procedures, characterization data, and copies of the ^{1}H NMR, ^{13}C NMR, and HRMS spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.06.082.

References and notes

1. Berkowitz, D. B.; Charette, B. D.; Karukurichi, K. R.; McFadden, J. M. *Tetrahedron: Asymmetry* **2006**, *17*, 869.
2. Lacoste, A. M.; Darriet, M.; Neuzil, E.; Le Goffic, F. *Biochem. Soc. Trans.* **1988**, *16*, 606.
3. Rando, R. R. *Biochemistry* **1974**, *13*, 3859.
4. Lai, J. C. K.; Cooper, A. J. L. *J. Neurochem.* **1986**, *47*, 1376.
5. Selvam, C.; Goudet, C.; Oueslati, N.; Pin, J.-P.; Acher, F. C. *J. Med. Chem.* **2007**, *50*, 4656.
6. Valiaeva, N.; Bartley, D.; Konno, T.; Coward, J. K. *J. Org. Chem.* **2001**, *66*, 5146.
7. Paleo, M. R.; Aurrecoechea, N.; Jung, K. Y.; Rapoport, H. *J. Org. Chem.* **2003**, *68*, 130.
8. Afzali-Ardakani, A.; Rapoport, H. *J. Org. Chem.* **1980**, *45*, 4817.
9. Hanessian, S.; Sahoo, S. P. *Tetrahedron Lett.* **1984**, *25*, 1425.
10. Pellicciari, R.; Natalini, B.; Marinozzi, M. *Synth. Commun.* **1988**, *69*, 1715.
11. Berkowitz, D. B.; Smith, M. K. *Synthesis* **1996**, 39.
12. Carrasco, M.; Jones, R. J.; Kamel, S.; Rapoport, H.; Truong, T. *Org. Synth.* **1992**, *70*, 29.
13. (a) Persson, T.; Hansen, T. H.; Rasmussen, T. B.; Skindersø, M. E.; Givskov, M.; Nielsen, J. *Org. Biomol. Chem.* **2005**, *3*, 253; (b) Bartley, D. M.; Coward, J. K. *J. Org. Chem.* **2005**, *70*, 6757.
14. Finkelstein, H. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 1528.
15. Emerson, D. W.; Korniski, T. J. *J. Org. Chem.* **1969**, *34*, 4115.
16. Sharpless, K. B.; Young, M. K. *J. Org. Chem.* **1975**, *40*, 947.